

## THE HÆMATOPOIETIC FUNCTIONS IN GENERAL PARESIS.

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In a disease with so widespread a seat as general paresis, in which the cerebral syphilitic changes are local manifestations of a generalized infection, it is only reasonable that an attempt should be made to correlate the cerebral changes with those found in other organs in the same body.

In reading descriptions of the histological findings in general paresis, it is striking to note the scarcity of references to the hæmatopoietic system. Yet these tissues certainly suffer, and the changes they undergo are fairly constant, and may be observed in the bone-marrow and inferred from examination of the blood.

For the observations described below specimens of marrow were prepared, consisting of sections and smears taken from ribs at autopsy. Lymphatic tissues were at the same time removed from various situations. The subjects were all patients who had died from paresis without any treatment likely to stimulate the hæmatopoietic functions.

The examination of the blood was made in a series of 50 patients in all stages of the disease who had not yet received treatment, and in 30 of the same subjects during treatment with relapsing fever, and six to nine months afterwards. The fever was induced by injection of the blood of mice infected with *Spirochaeta Obermeieri*. As no death occurred among those so treated, it was not possible to examine the marrow or lymphatic tissues of the same cases.

### UNTREATED PARESIS.

*Lymphatic tissues* presented the usual slight changes described in connection with syphilis, so far as the glands, tonsils, thymus and spleen were concerned.

*Bone-marrow.—Ribs :* To the naked eye the marrow was bright red. Little change was noted in the trabeculæ except slight thickening and fibrosis in some instances. The detached cells, however, showed notable changes. There was a marked scarcity of polymorphocytes. A diminution in number of the myeloblasts and myelocytes was a conspicuous feature. No changes were noticed in the number or form of the normoblasts or red cells.

These features were absent in 8 non-paretic syphilitic cases.

*Long bones :* The marrow showed nothing abnormal.

*Blood.—*There were no obvious numerical or morphological changes in the red cells until late in the disease, when the numbers fell to four or even three million. For some time the white count was normal, with a Schilling index of about 5%, but when wasting and weakness were apparent the total leucocytes showed a slight but progressive decline in numbers, with a rise in the Schilling index.

Paresis, middle stage :

Leucocytes . . . . .	5,000—6,000
Polymorphs . . . . .	63·5%
Eosinophils . . . . .	2%
Mast-cells . . . . .	0·5%
Small lymphocytes . . . . .	29%
Large „ . . . . .	2·5%
Monocytes . . . . .	2·5%

During the pyrexial periods there was often a slight absolute lymphocytosis. In some cases, however, only the neutrophil cells were increased, owing, no doubt, to intercurrent infection.

Paresis, pyrexial attack :

Leucocytes . . . . .	8,000
Polymorphs . . . . .	54%
Eosinophils . . . . .	3%
Mast-cells . . . . .	0·5%
Small lymphocytes . . . . .	37%
Large „ . . . . .	2·5%
Monocytes . . . . .	3%

#### THE BLOOD IN RELAPSING FEVER.

Little reference is made in the literature to the changes in the blood in patients contracting the disease in the usual manner. Polynuclear leucocytosis and a slight rise in the number of large mononuclear cells are mentioned.

## THE BLOOD IN RELAPSING FEVER ASSOCIATED WITH PARESIS.

*The red cells* numbered about five million. An occasional normoblast was seen, and there was slight variation in the size of the red cells. These changes were not found in paresis apart from pyrexial treatment.

Only an occasional red cell exhibited reticulation in films stained with cresyl blue.

*The white cells :*

At the beginning of pyrexia—

Leucocytes . . . . .	10,000
Polymorphs . . . . .	75%
Eosinophils . . . . .	1%
Mast-cells . . . . .	0·5%
Small lymphocytes . . . . .	6%
Large „ . . . . .	6%
Mononuclears . . . . .	11·5%

Middle of pyrexial period—

Leucocytes . . . . .	12,000
Polymorphs . . . . .	80%
Eosinophils . . . . .	0·5%
Mast-cells . . . . .	0·0·25%
Small lymphocytes . . . . .	5%
Large „ . . . . .	6%
Monocytes . . . . .	7%
Myelocytes . . . . .	1-1·5%

The total leucocyte count followed closely the course of the fever. At the onset of the first paroxysm the total rose to 9,000 to 10,000 owing to a numerical increase in polynuclears and mononuclears. At the height of the fever the total reached 12,000 owing to a further flooding of the circulation with polynuclears, accompanied by a relative fall in mononuclears. During the interpyrexial periods the numbers were maintained at about 5,000 in normal proportions.

In advanced stages of paresis there was little or no leucocytic reaction.

*Polymorphocytes* constituted the bulk of the supernumerary cells. At the beginning of the leucocytosis as many as 25% of the neutrophil granular cells were metamyelocytes—that is to say, immature polymorphocytes—while towards the end of the pyrexia the percentage rose to 50-65%.

A few neutrophil myelocytes were present.

The cells varied greatly in size, exceptionally large forms being frequently seen, with excessively mature nuclei.

At the end of the fever, in favourable cases, when the number of cells fell to normal, the proportion of immature neutrophils fell gradually, reaching normal a few weeks later.

*The lymphocytes* included an unusual number of the large variety. The nucleus varied greatly in size, but stained well with Leishman's and Pappenheim's stains. In many cells the cytoplasm, which took on a darker stain than that of the monocytes, was plentiful, and in several it contained fine basophil granules.

*The mononuclear cells* reached about 10% at the beginning of the fever. Great variations in size were observed, many cells having the diameter of a medium-sized neutrophil. In the majority the nucleus was well notched or reniform, but in many the notching was slight. In one cell there was a double notch, the two nearly meeting in the middle and almost dividing the nucleus into two equal parts. The contour of the cytoplasm was rounded. Two cells were noticed in which the double notching had resulted in complete bisection of the nucleus, the cytoplasm in both cells being clear and pale blue, with an oval outline, the long sides of which presented an indentation which was suggestive of the division of a parent-cell into two.

Many cells contained a few neutrophil granules. Towards the end of the fever the number of monocytes fell before that of the polymorphocytes.

*The eosinophil cells* showed no appreciable change in form or numbers, except that they were reduced numerically at the end of the fever and that there was no post-infective increase.

*Neutrophil myelocytes* appeared in small numbers, and an occasional eosinophil myelocyte was seen. No myeloblasts were observed with certainty.

*Mast leucocytes* were scanty. They were medium-sized, with usually a tripartite nucleus, the whole cell being studded with coarse basophil granules.

#### THE BLOOD SIX MONTHS AFTER INFECTION WITH RELAPSING FEVER.

From a therapeutic point of view the results of treatment were disappointing. Four cases showed some mental and physical improvement. These yielded a higher percentage of polymorphocytes after this interval than did the others. It was found that in those patients whose decline proceeded steadily in spite of treatment, the granular cells were abnormally few and most of them immature. In fact, the progress of the disease appeared to have been hastened by fever treatment, and the same results were

obtained with other methods of inducing pyrexia. With a good leucocytic response slight benefit resulted; with a poor response harm was done.

A satisfactory case nine months after treatment :

Leucocytes	. . . . .	6,000
Polymorphs	. . . . .	65%
Eosinophils	. . . . .	2%
Mast-cells	. . . . .	0
Small lymphocytes	. . . . .	26%
Large	” . . . . .	2%
Monocytes	. . . . .	5%

A poor result :

Leucocytes	. . . . .	4,000
Polymorphs	. . . . .	50·5%
Eosinophils	. . . . .	3%
Mast-cells	. . . . .	1·5%
Small lymphocytes	. . . . .	34%
Large	” . . . . .	5%
Monocytes	. . . . .	6%

#### THE RELATIONSHIP OF THESE CHANGES TO PATHOGENESIS.

It is conceivable that the depression of the blood-forming function described above may play some part in determining whether a syphilitic subject will develop paresis. The cerebral lesions in general paresis consist of—

- (1) Meningo-vascular changes and—
- (2) Neuronal degeneration.

As regards the parenchymatous changes in spinal cord and medulla the posterior columns are most obviously affected, yet careful search will, in nearly all cases, demonstrate degenerative changes in the lateral, antero-lateral and postero-lateral tracts. The distribution and type\* are almost identical with those of the lesions found in subacute combined degeneration. It is suggested, therefore, that the pathological findings in the blood and blood-forming tissues, together with the distribution of the parenchymatous changes in paresis, bear a close analogy to a somewhat similar condition in pernicious anæmia, and that the attack upon the reticulo-endothelium by the syphilitic virus is one of the factors which determine the occurrence of paresis in a syphilitic subject.

Severe anæmia occurs in tertiary syphilis in association

\* The lesions are circumscribed; they are non-inflammatory, as they do not shade off at the edges, and non-systemic, as they are not continued up or downwards.

sometimes with hepatic involvement (1). In congenital syphilis a definitely hypoplastic myeloid reaction may be found in the marrow (2).

It is sufficient to say, therefore, that profound changes may occur in the hæmatopoietic tissues in syphilis.

A further point of interest is the resemblance of early paresis to hyperthyroidism, as regards signs and symptoms, and the presence in exophthalmic goitre of lymphoid deposits in the body associated with lymphocytosis in the cerebro-spinal fluid, bearing in mind the probable endocrine control of the adult blood-forming organs.

It is not suggested that the failure of a portion of the reticulo-endothelium is entirely responsible for the accumulation of spirochætes in large numbers in the cortex in the manner peculiar to general paresis, but it is reasonable, on the above hypothesis, to consider the possibility of the cerebral neuronal tissues being thereby depressed in their vitality, as in pernicious anæmia, to such an extent that the syphilitic virus is enabled to invade, flourish in, and destroy these tissues.

#### GENERAL CONSIDERATIONS.

The exhaustion of the leucogenic function of the reticulo-endothelium, proportionate to the stage to which the paresis has advanced, implies a break-down in the cellular forces of resistance so far as a polymorphocytosis is concerned. This may partly account for the readiness with which paretic patients suffer from bed-sores and succumb to intercurrent infection.

In modern pyrexial therapy, the only effect, apart from the fever, appears to be to stimulate a leucocytosis or, in some cases, a lymphocytosis. Considerable attention has been paid to the pyrexia, but apparently none to the depressed reticulo-endothelium.

It would appear somewhat futile to over-stimulate an already exhausted tissue, and the rationale of pyrexial treatment should be to stimulate these functions at a time when this means of combating infection, associated as it is with the production of fever, would be more likely to be successful. This should be in the earliest stages of paresis, as is well recognized, or better still, employed as a preventive measure in the tertiary or secondary stages.

The selection of cases of developed paresis should be controlled by making a preliminary test with sodium nucleinate or some other mild leucogenic agent in order to avoid applying drastic pyrexial treatment to those cases which have a poor leucocytic response.

The more beneficial effects of induced malaria are interesting in

view of the fact that a leucopenia is produced so far as the polymorphocytes are concerned. It is possible that the rest afforded to the leucoblastic tissues allows of some regeneration.

#### CLINICAL NOTE REGARDING RELAPSING FEVER.

Twenty-four to forty-eight hours after the injection an initial rise of temperature occurred to 100° F., probably the result of the introduction of foreign protein. On the third or fourth day the first paroxysm occurred. The pyrexial periods and the interpyrexial intervals were, in most cases, of five days' duration, and followed the ordinary clinical course. There were, however, a number of abortive attacks. Although the blood of the mice teemed with organisms, they were very scanty in that of the patients.

One point of interest was that two of the patients presented a transient facial palsy of the lower neuron type.

#### SUMMARY.

In general paresis there is impairment of the function of the leucoblastic tissues in the bone-marrow, with diminution of the leucocyte reserve. This is not the case in non-paretic syphilis.

General paresis is differentiated from other forms of cerebral syphilis by the nature of the parenchymatous changes in the central nervous system. The affection of the blood-forming tissues constitutes another differentiating factor. It is possible that this condition is one which depresses the cerebral tissues and weakens their resistance to the attacks of the spirochætes.

An analogy can be drawn between paresis and pernicious anæmia, in that—

(1) There is, in both, impairment of the blood-forming tissues, and—

(2) The distribution of the degenerated areas in the medulla and spinal cord is suggestively similar in both.

The depression of leucopoietic activity may account for the ease with which bed-sores are developed in paretic subjects, and the readiness with which the patients die of intercurrent infection.

When some infection is induced in a paretic which will excite polymorphocytosis, the circulation immediately receives a high proportion of immature leucocytes.

The degree of leucocytic reaction induced by infection with *Spirochæta Obermeieri* or other leucogenic agents varies inversely with the stage to which the general paresis has advanced.

The better the general condition of the patient after such pyrexial

treatment the nearer does the differential count approach the normal, and the converse is equally true.

The progress of general paresis can sometimes be stayed by measures which result in increased leucogenesis.

On the other hand, these measures tend to hasten the progress of the disease in cases which produce an unfavourable leucocytic response.

With regard to induced malaria, which, so far as the polymorphocytes are concerned, produces leucopenia, it is significant that a condition which gives the leucopoietic tissues a rest should be associated with a clinical improvement.

It is suggested that when pyrexial therapy of a leucogenic type is contemplated, a preliminary test should be carried out in order to eliminate those cases which give a poor leucocytic response, since these cases are apt to deteriorate under such treatment.

#### HISTOLOGICAL METHODS EMPLOYED.

Differential blood-counts . . .	Leishman's stain (Gruebler).
Reticulated red cells . . .	Cresyl blue.
Nuclear differentiation . . .	Pappenheim's nuclear stain.
Reticulo-endothelial tissue . . .	Hortega's silver method.

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*References.*—(1) Hoppe-Seyler, *Med. Clin.*, 1914.—(2) Zanca, *Arch. de Méd. des Enf.*, 1926, p. 505.